Claims

1. A method for inhibiting the formation of intracellular aggregates of selected polypeptides comprising, the step of contacting said polypeptide capable of forming said aggregates with a polypeptide-binding molecule that specifically binds to said polypeptide in a manner to minimize aggregation, thereby inhibiting the formation of said intracellular aggregates.

2. The method of claim 1, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Prion protein, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

3. The method of claim 1, wherein said polypeptide comprises a naturally-occurring polypeptide having additional glutamine residues as compared to the corresponding wild type polypeptide.

4. The method of claim 1, wherein said polypeptide is the huntingtin polypeptide.

5. The method of claim 1, wherein said polypeptide is the huntingtin polypeptide comprising additional glutamine residues as compared to the corresponding wild type huntingtin polypeptide.

6. The method of claim 1, wherein said polypeptide is Tau.

7. The method of claim 1, wherein said polypeptide-binding molecule is selected from the group consisting of small molecules, peptides, peptidomimetics, antibodies, antibody fragments, and intrabodies.

8. The method of claim 1, wherein said polypeptide-binding molecule is an intrabody.

9. The method of claim 8, wherein said intrabody is monovalent.

10. The method of claim 8, wherein said intrabody specifically binds to the amino-terminal residues 1-17 of huntingtin polypeptide.

11. The method of claim 8, wherein said intrabody specifically binds an epitope exclusive of polyglutamine.

12. The method of claim 8, wherein said intrabody is multivalent.

13. The method of claim 8, wherein said intrabody comprises a spacer region.

14. The method of claim 8, wherein said intrabody comprises an amino acid sequence corresponding to ubiquitin.

15. The method of claim 14, wherein said intrabody retargets the polypeptide to a proteasome.

16. The method of claim 8, wherein said intrabody comprises an amino acid sequence corresponding to a targeting signal.

17. The method of claim 16, wherein said intrabody retargets the cellular location of the polypeptide.

18. The method of claim 16, wherein said targeting signal is cytoplasmic, nuclear, lysosomal, plasma membrane-associated, endoplasmic reticulum-associated, peroxisomal, or proteosomal.

19. The method of claim 16, wherein said targeting signal is nuclear.

20. The method of claim 16, wherein said targeting signal is lysosomal.

21. The method of claim 8, wherein said intrabody comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

22. The method of claim 8, wherein said intrabody comprises the amino acid sequence of α-Nt-HD-C4 sFv provided in SEQ ID NO: 6.

23. The method of claim 8, wherein said polypeptide is contacted with said intrabody *in vivo*.

24. A method for inhibiting the formation of intracellular aggregates of selected polypeptides in a subject comprising, administering to said subject at risk of having said

intracellular aggregates, an polypeptide-binding molecule which specifically binds to said polypeptide in a manner to minimize aggregation thereby inhibiting the formation of said intracellular aggregates.

25. The method of claim 24, wherein said subject is at risk for a neurological disease.

26. The method of claim 25, wherein said subject is at risk for neurological disease-associated diabetes.

27. The method of claim 24, wherein said subject is a human.

28. The method of claim 24, wherein said subject is an experimental animal.

29. The method of claim 28, wherein said subject is a Huntington's disease animal model.

30. The method of claim 24, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

31. The method of claim 24, wherein said polypeptide comprises a naturally-occurring polypeptide having additional glutamine residues as compared to the corresponding wild type polypeptide.

32. The method of claim 24, wherein said polypeptide is the huntingtin polypeptide.

33. The method of claim 24, wherein said polypeptide is the huntingtin polypeptide comprising additional glutamine residues as compared to the corresponding wild type huntingtin polypeptide.

34. The method of claim 24, wherein said polypeptide is Tau.

35. The method of claim 24, wherein said polypeptide-binding molecule is selected from the group consisting small molecule, peptide, peptidomimetic, antibody, antibody fragment, and intrabody.

36. The method of claim 24, wherein said polypeptide-binding molecule is an intrabody.

37. The method of claim 36, wherein said intrabody is administered as a nucleic acid expressible in said subject.

38. The method of claim 36, wherein said intrabody comprises the amino acid sequence of -anti-Nt-HD- C4 sFv provided in SEQ ID NO: 6.

39. A method for treating a subject having, or likely to have, a neurological disorder comprising, administering to said subject an polypeptide-binding molecule which specifically binds a polypeptide capable of forming a polypeptide aggregate associated with a neurological disorder thereby inhibiting said aggregate from forming.

40. The method of claim 39, wherein said neurological disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Prion disease, FTD, ALS, SBMA, DRPLA, SCA1, SCA2, SCA3/MJD, SCA4, SCA5, SCA6, and SCA7.

41. The method of claim 39, wherein said neurological disorder is Huntington's disease.

42. The method of claim 39, wherein said neurological disorder is Huntington's disease-associated diabetes.

43. The method of claim 39, wherein said neurological disorder is Alzheimer's disease.

44. The method of claim 39, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

45. The method of claim 39, wherein said polypeptide comprises a naturally-occurring polypeptide having additional glutamine residues as compared to the corresponding wild type polypeptide.

46. The method of claim 39, wherein said polypeptide is the huntingtin polypeptide.

47. The method of claim 39, wherein said polypeptide is the huntingtin polypeptide comprising additional glutamine residues as compared to the corresponding wild type huntingtin polypeptide.

48. The method of claim 39, wherein said polypeptide is Tau.

49. The method of claim 39, wherein said polypeptide-binding molecule is selected from the group consisting small molecule, peptide, peptidomimetic, antibody, antibody fragment, and intrabody.

50. The method of claim 39, wherein said polypeptide-binding molecule is an intrabody.

51. The method of claim 50, wherein said intrabody is administered as a nucleic acid expressible in said subject.

52. The method of claim 41, wherein said intrabody comprises the amino acid sequence of anti-Nt-HD C4 sFv provided in SEQ ID NO: 6.

53. A method for identifying an polypeptide-binding molecule or a functional fragment thereof which specifically recognizes a polypeptide capable of forming intracellular polypeptide aggregates comprising,

providing a polypeptide capable of forming intracellular polypeptide aggregates;

contacting said polypeptide with a test polypeptide-binding molecule intrabody or functional fragment thereof; and

determining the ability of said test polypeptide-binding molecule intrabody or functional fragment thereof to specifically recognize said polypeptide,

thereby identifying an polypeptide-binding molecule which specifically recognizes a polypeptide capable of forming intracellular polypeptide aggregates.

54. The method of claim 53, wherein said polypeptide-binding molecule is selected from the group consisting small molecule, peptide, peptidomimetic, antibody, antibody fragment, and intrabody.

55. The method of claim 53, wherein said polypeptide-binding molecule is an intrabody.

56. The method of claim 53, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

57. The method of claim 53, wherein said polypeptide comprises a naturally-occurring polypeptide having additional glutamine residues as compared to the corresponding wild type polypeptide.

58. The method of claim 53, wherein said polypeptide is the huntingtin polypeptide.

59. A method for identifying a compound which specifically recognizes a polypeptide capable of forming undesired intracellular polypeptide aggregates comprising,

providing a polypeptide capable of forming intracellular polypeptide aggregates;

providing a test intrabody or functional fragment thereof that binds said polypeptide;

incubating said polypeptide and intrabody fragment or fragment thereof with a binding molecule; and

determining the ability of said test compound to alter the binding of said intrabody or functional fragment thereof, wherein those binding molecules that bind the intrabody are eliminated,

thereby identifying said test compound as capable of interacting with a polypeptide capable of forming intracellular polypeptide aggregates.

60. The method of claim 59, wherein the steps of the method are repeated for a variegated library having a complexity selected from the group consisting of 10^2, 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, and 10^9 different binding molecules.

61. The method of claim 59, wherein the steps of the method are repeated for a variegated library having a complexity of at least 10^9 different binding molecules.

62. The method of claim 59, wherein the test compound is selected from the group consisting of small organic molecules, peptides, and natural product extracts.

63. The method of claim 59, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin,

Apolipoprotein, α-Synuclein, huntingtin, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

64. The method of claim 59, wherein said polypeptide comprises additional glutamine residues as compared to the wild type polypeptide.

65. The method of claim 59, wherein said polypeptide is the huntingtin polypeptide.

66. The method of claim 59, wherein said polypeptide is the huntingtin polypeptide comprising additional glutamine residues as compared to wild type huntingtin polypeptide.

67. The method of claim 59, wherein said polypeptide is Tau.

68. An isolated nucleic acid molecule encoding an intrabody, or functional fragment thereof, which binds to a selected polypeptide capable of forming intracellular polypeptide aggregates associated with a neurological disorder.

69. The molecule of claim 68, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Prion protein, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

70. The molecule of claim 68, wherein said polypeptide comprises a naturally-occurring polypeptide having additional glutamine residues as compared to the corresponding wild type polypeptide.

71. The molecule of claim 68, wherein said polypeptide is the huntingtin polypeptide.

72. An intrabody, or functional fragment thereof, which binds to a selected polypeptide capable of forming intracellular polypeptide aggregates associated with a neurological disorder.

73. The molecule of claim 72, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Prion protein, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

74. The molecule of claim 72, wherein said polypeptide comprises a naturally-occurring polypeptide having additional glutamine residues as compared to the corresponding wild type polypeptide.

75. The molecule of claim 72, wherein said polypeptide is the huntingtin polypeptide.

76. The molecule of claim 72, wherein said polypeptide is the huntingtin polypeptide comprising additional glutamine residues as compared to the corresponding wild type huntingtin polypeptide.

77. The molecule of claim 72, wherein said polypeptide is Tau.

78. A method for inhibiting the formation of intracellular aggregates of a selected polypeptide in animal comprising,

immunizing said animal with an immunogen having an epitope in common with said selected polypeptide, wherein said immunizing provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of said selected polypeptide to occur.

79. The method of claim 78, wherein said animal is a human.

80. The method of claim 78, wherein said polypeptide is selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Prion protein, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

81. The method of claim 80, wherein said polypeptide comprises a naturally-occurring polypeptide having additional glutamine residues as compared to the corresponding wild type polypeptide.

82. The method of claim 80, wherein said polypeptide is the huntingtin polypeptide.

83. The method of claim 80, wherein said polypeptide is the huntingtin polypeptide comprising additional glutamine residues as compared to the corresponding wild type huntingtin polypeptide.

84. The method of claim 80, wherein said polypeptide is the Amyloid Precursor Protein.

85. The method of claim 78, wherein said immunogen is a polypeptide comprising an epitope in common with a polypeptide selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Prion protein, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

86. The method of claim 85, wherein said polypeptide is Huntington.

87. The method of claim 78, wherein said immunogen is an expressible nucleic acid vaccine encoding a polypeptide comprising an epitope in common with a polypeptide selected from the group consisting of Amyloid Precursor Protein, Presenilin 1, Presenilin 2, α-2 Macroglobulin, Apolipoprotein, α-Synuclein, huntingtin, Prion protein, Tau, SOD, AR, Atrophin 1, Ataxin 1, Ataxin 2, Ataxin 3, CACNL1A4, and SCA7.

88. The method of claim 87, wherein said polypeptide is Huntington.

89. The method of claim 87, wherein said polypeptide is Tau.

90. The method of claim 78, wherein said animal has, or is at risk for having, Huntington's disease.

91. The method of claim 78, wherein said animal has, or is at risk for having, Huntington's associated diabetes.

92. The method of claim 78, wherein said animal has, or is at risk for having, high fasting blood glucose levels.

93. The method of claim 78, wherein said animal has, or is at risk for having, low insulin levels.